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Quarterly Progress Report Number 3

Transcutaneous Analyte Measuring Methods
(TAMM Phase II)

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Biotronics Technologies, Inc.

March, April, May, 1992

Naval Medical Research and Development Command

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(TAMM Phase II)

Prepared by
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Abstract

The major objective of the third quarter of the project, the completion and delivery of the two BI-800 Array Analyzers, was accomplished. Both spectrometers were delivered on June 1, one to the Naval Medical Research and Development Command in Bethesda, Maryland, and the second to the Medical College of Wisconsin (Froedtert Lutheran Memorial Hospital). Clinical testing using the BI-800 systems is scheduled to begin in June (22nd) in Bethesda and by July 15th in Milwaukee.

A significant effort has been devoted to developing operational procedures for TAMM/800. These procedures were developed at two levels:

1. The test sequence level

   Measurements to be performed at various body locations and reference standards

2. The instrument operation level

   The procedures for instrument operation

Both kinds of procedures are reviewed in this quarterly report.

Another important area of project activity currently is analytical data reduction. An integrated set of software programs is being developed to analyze the data generated in clinical trials. These programs will allow for the development of algorithms for analyte concentration estimations and the evaluation of their accuracy and tracking capability. This report also provides detail on this software development.

Clinical Test Procedure

The clinical test procedure planned for execution in both Bethesda and Milwaukee is detailed below. Four separate skin surface measurements involving multiple spectral scans will be made on the wrist (vein), wrist (reference), arm (capillary) and neck (artery). A wavelength calibration scan will be performed followed by an optical reflectance standard measurement.

A. Patient Greeting

   1. Briefly discuss objectives of the test and possible impact on the patient
   2. Input patient information into the patient's file

B. First Reading: right wrist scan (vein)

   1. Prepare the computer for the first scan
   2. Swab patient's right wrist with alcohol
   3. Swab the optrode with alcohol
   4. Place the optrode over the pulse point on the patient's right wrist (the dominant vein)
   5. Initiate the first scan
   6. Complete the first scan

C. Second Reading: right wrist scan (reference)

   1. Select the next reading (scan setting) on the computer
   2. Swab the patient's right wrist with alcohol

3. Swab the optrode with alcohol
4. Place the optrode over the Flexor Pillicis Longus
5. Initiate the second scan
6. Complete the second scan

D. Third Reading: right forearm scan (capillary-interstitial fluid)

1. Select the next reading on the computer
2. Swab the patient's right forearm with alcohol
3. Swab the optrode with alcohol
4. Place the optrode on the inside of the forearm, specifically over the Brachioradialis
5. Initiate the third scan
6. Complete the third scan

E. Fourth Reading: neck scan (artery)

1. Select the next reading on the computer
2. Swab the patient's neck with alcohol
3. Swab the optrode with alcohol
4. Place the optrode over the pulse point on the neck
5. Initiate the fourth scan
6. Complete the fourth scan

F. Wavelength Calibration Scan

G. High Reflective Standard Scan

Instrument Operation Procedures

The TAMM BI-800 operation is controlled from a PC-type microcomputer. These procedures embrace computer setup, new patient data entry, reading (measurement) sequence, spectral plotting and data storage. These procedures developed during the past reporting period are included in Appendix I.

Analytical Data Reduction

Clinical data will be processed through a series of programs that formulate and test algorithms for their capability to estimate blood analyte concentrations based on near infrared spectral data. These programs may be classified into two areas: spectral preprocessing and pattern recognition analysis. Spectral preprocessing programs convert raw spectral data into a form suitable for pattern recognition analysis. Pattern recognition programs provide the actual estimates of analyte concentrations from preprocessed inputs.

Some of the data processing functions now being developed in each of these two categories are listed below:

Spectral preprocessing

1. Pre-Filtering of Spectral Intensity Outputs

   a. Median filter
   b. Fourier filter
   c. Wiener-Kalman filter

2. **Absorbance Determination**

$$A = -\log_{10} (I_\lambda / I_{ref})$$

where

I_λ - light intensity at wavelength λ
I_{ref} - light intensity at reference wavelength λ_{ref} or reference standard

3. **Spectral Smoothing**

Savitsky-Golay smoothing

4. **Principal Components**

a. in eigenvector order

b. single rotated component for each analyte

Pattern recognition analysis

1. Genetic neural network (NETGEN)
2. Liquid Correlation Analysis (LCA)
3. Lattice Nearest Neighbor (K-NN) analysis
4. Multiple discriminant analysis

Plans for Next Reporting Period

Current plans call for the completion of clinical testing by the end of the next quarter (September 30, 1992). Preliminary analysis results on algorithm selection and accuracy performance should also be available.

Kenneth J. Schlager
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APPENDIX I.

Subj: Computer Procedure for TAMM BI-800 NIR Array Analyzer Testing

Date: June 19, 1992

Instructions for setting up the computer and using it in conjunction with the TAMM BI-800 NIR Array Analyzer to complete noninvasive skin measurement tests are provided below.

Characters to be typed into the computer by the operator are in *italics* in the text. Keyboard buttons to be pressed are set off by the following symbols: < >, e.g., <Enter>. Items on the screen can be selected either by clicking on them with a mouse or by highlighting them by using the arrow keys and then pressing <Enter>.

Menus from the menu bar (which offers the following selections: Operator, Data Entry, Technician, Quit) can be opened by clicking on them or by highlighting them and pressing <Enter>. Menu items can be selected in the same manner.

Computer Setup

1. Power-up the computer.

2. Power-up both BI-800 units.

3. Change from the root directory (C:\) to the TAMM directory: *cd\tamm <Enter>*.

4. Start the TAMM software by typing the following at the prompt: *tamm <Enter>*.

5. Wait for the software to load the configuration files.

6. At the computer prompt to press any key, do so.

7. Insert a 5 1/4" patient diskette into drive A of the computer.

Entering New Patient Data

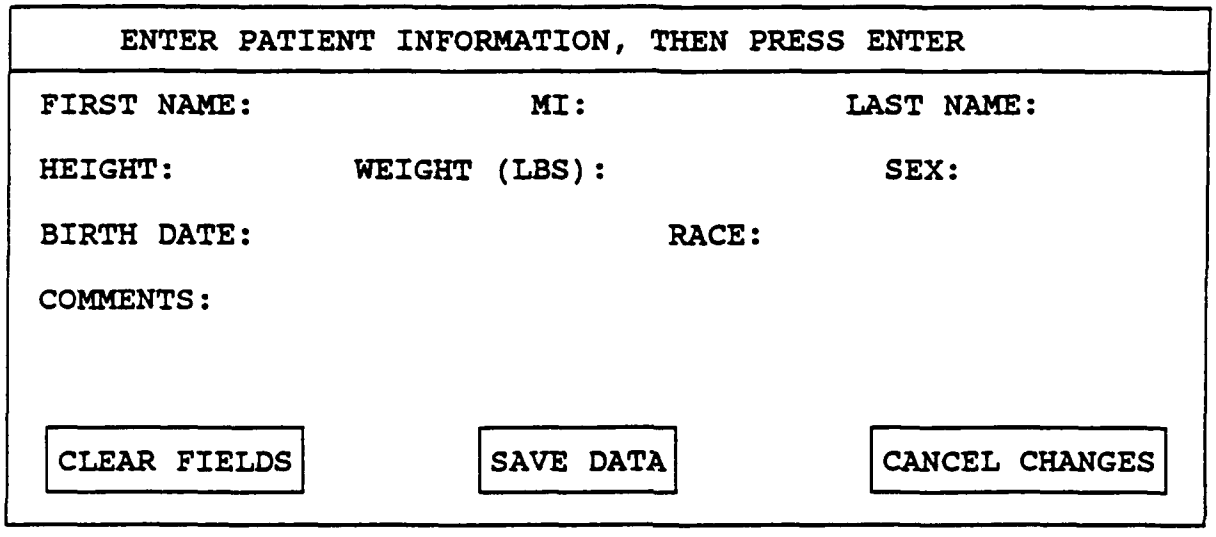
1. From the menu bar at the top of the screen, open the **Operator** menu and select **Patient Information.**

2. Click on **Clear Fields** before entering information in the form that appears on the screen.

3. Fill in the information requested for each field (see Figure) by clicking on the field to be filled and then entering the information.

   The name of the patient does not have to be entered. Instead, insert XXX for **First Name**, X for **MI** and XXX for **Last Name**.

   In the **Comment** field, enter the name of any medication the patient is taking, whether there are any moles, blemishes or scars of the patient's skin in the area where the scan will be taken, and any other pertinent information.



4. After entering all the information you must select **Save Data** from the bottom of the screen to exit.

   Check to make sure the patient number in the upper right-hand corner of the screen changes when **Save Data** is selected.

Loading Information from an Earlier Patient

1. Insert the diskette containing the information for the patient of interest into drive A.

2. From the menu bar at the top of the screen, open the **Data Entry** menu and select **Load Patient**.

3. If the information from the diskette is successfully loaded, the message "Patient file loaded" will appear.

4. If the information cannot be loaded, the message "ERROR - Can't find patient file on disk in drive A" will appear.

The error message may appear if the information was not correctly saved onto the diskette when the patient was scanned, or if information from more than one patient has been stored on the diskette.

Reading Sequences

1. Prepare the computer for a scan sequence by opening the **Operator** menu and selecting **Begin Read Sequence.**

2. Follow the directions that appear on the screen.

3. Check the read number to make sure that the patient is prepared for the corresponding reading, as described in the **Clinical Procedure** sheet.

4. Select **Begin.**

5. Wait for reading to be completed.

6. Select **Next** to set up for next reading.

   NOTE: If **Next** is not pressed, the last completed scan will be written over.

   NOTE: Selecting **Redo** will cause the previous scan to be overwritten.

7. Repeat steps 2 through 6 until all four patient readings have been completed.

   NOTE: Pressing <Esc> will interrupt the scan if an error was made during the scan, e.g., if the fiber was moved or lifted from the skin.

   NOTE: **Prev** can be used if a read scan was accidentally skipped over

8. Complete two reflectance standards.

   a. Uncover the **Wavelength** setting on the Reflectance Standards Box.

   b. Attach the fiber and **hold** it in place on the box.

   c. Follow steps 2 through 6.

   d. Detach the fiber from the box.

   e. Replace the cover on the setting on the Reflectance Standards Box.

f. Uncover the **High** setting on the box.

g. Follow steps b through e.

NOTE: The high reflectance standard is **read 9 of 9.**

9. Select **Cancel** once all four patient readings and the two standard readings have been completed.

10. Click on **Okay** when the message "Read Sequence Aborted by User" appears.

11. Wait for scans to be saved to the diskette.

Plotting Spectra on Screen

1. To plot the spectra from a read sequence on the screen, open the **Technician** menu and select **Password.** Type the password *BTI* (use all capital letters for the password).

   NOTE: The password only needs to be entered once each time the unit is powered-up.

   NOTE: Do not use **Graph** from the **Read Sequence** screen to obtain plots of the spectra for a patient. **Graph** will only plot the spectra for the last scan taken.

2. Open the **Technician** menu and select **Load Plot Spectra.**

3. Wait for the spectra to be loaded.

4. After the spectra are loaded, open the **Technician** menu and select **Plot Spectra on Screen.** The plot of the first reading will be graphed.

5. Click on (and darken) **Sub**, **Absorb**, and **Grid** located along the right side of the screen, if they have not already been darkened.

6. To obtain plots of all the readings and standards, click to the left of the first five and the ninth of the labeled boxes in the top right corner of the screen. The boxes are labeled to match the scans performed.

7. Click on and darken **Dw**, if it has not already been darkened.

8. Make sure all plots of the four patient scans and two reflectance standard scans are on the screen.

9. Check to make sure that all four patient scan absorbance spectra are similar in shape.

Patient Follow-Up After Reading Sequences Are Completed

1. Record the patient code (located in the upper right portion of the computer screen) on the patient disk.

2. Record the patient code on the blood vial and on the laboratory paperwork.

3. Remove diskette.

Exiting

To exit, select **Quit** from the menu bar.